

**REMARKS**

It has come to our attention that an error is found in the relaxin-3 b-chain amino acid sequence represented by SEQ ID NO:3 in the Substitute Sequence Listing submitted June 14, 2006. A "Ser" residue at position 25 has inadvertently been omitted from this sequence. The enclosed second Substitute Sequence Listing corrects this omission by insertion of the missing "Ser at position 25 of SEQ ID NO:3.

Support for this correction may be found in prior art publicly available as of the June 20, 2003 priority date, copies of which are enclosed for the convenience of the Examiner. Relevant pages from PCT published application WO 03/030930 contain reference to relaxin H3 B chain as SEQ ID NO:2 on page 4, lines 10-16; page 5, lines 4-10; pages 5, line 31, through page 6, line 6; page 16, lines 1-7; page 17, lines 19-25; page 19, lines 1-5; page 20, lines 1-7; Fig. 1A, "B Chain"; Fig. 2A, "B Chain Aligns", "Human 3"; and "SEQUENCE LISTING", page 1/6, "H3-B chain", SEQ ID NO:2, where the "Ser" residue at position 25 is present.

In addition, copies of GenBank Accession No. Q8WXF3 and the corresponding entries from the UniProt/Swiss-Prot database showing sequence submission before the June 20, 2003 priority date are included. The GenBank entry also describes the region of the relaxin 3 preproprotein from amino acid positions 26-52 as "processed active peptide" and the "FEATURE" section of the UniProtKB Entry Q8WXF3 includes a "PEPTIDE" described as "Relaxin-3 B chain", each with the "Ser" at position 25 in agreement with the amino acid sequence of the corrected version of SEQ ID NO:3.

This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-25, in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Appl. No. 10/561,304

PATENT

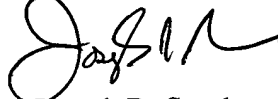
Amdt. dated March 19, 2007

Reply to Notification of Missing Requirements of March 16, 2006

Supplemental Preliminary Amendment

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Snyder", is written over the typed name.

Joseph R. Snyder

Reg. No. 39,381

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Attachments

JRS:dmw

60999674 v1

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PCT

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(25) Filing Language: English

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(84) Designated States (*regional*): ARIPO patent (GH, GM,  
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
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TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

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**Published:**

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*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: HUMAN 3 RELAXIN

(57) Abstract: Human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues having a modified A chain and/or a modified B chain are described. Also described are nucleic acid sequences encoded human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues. Also described are methods for the treatment of conditions responsive to administration of H3 relaxin or analogues thereof.



WO 03/030930 A1

- 4 -

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser  
 1 5 10 15

5 Lys Ser Glu Ile Ser Ser Leu Cys  
 20

(SEQ ID NO: 4)

or an amino acid sequence truncated by up to about 9 amino acids from N-terminus,

10 the B chain having the amino sequence:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
 1 5 10 15

15 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
 20 25

(SEQ ID NO: 2)

or an amino acid sequence truncated by up to 9 amino acids from the amino-terminus  
 and/or up to about 5 amino acids from the carboxyl-terminus,

20

the A and B chains being linked by interchain disulphide bonds at A11-B10, and A24-B22,  
 and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity.

In a third aspect of the invention there is provided a composition comprising a human H3  
 25 relaxin analogue having a modified A chain and/or a modified B chain,

the H3 relaxin A chain having the amino acid sequence:

30 Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser  
 1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys  
 20

(SEQ ID NO: 4)

- 5 -

wherein the carboxyl-terminus is an amide derivative and/or Lys at position 12 is replaced with Glu, and/or Glu at position 19 is replaced with Gln,

the H3 relaxin B chain having the amino acid sequence:

5  
 Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
 1 5 10 15  
 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
 10 20 25 (SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

15 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22 and wherein the human H3 relaxin analogue has relaxin bioactivity.

In accordance with a fourth aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B  
 20 chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

the A chain comprising:  
 25  
 Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser  
 1 5 10 15  
 Lys Ser Glu Ile Ser Ser Leu Cys  
 30 20 (SEQ ID NO: 4)

the B chain comprising:

- 6 -

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
 1 5 10 15

5 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
 20 25 (SEQ ID NO: 2)

the signal sequence comprising:

10 Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Leu Thr  
 1 5 10 15

Gly Glu Leu Trp Pro Gly Ala Glu Ala  
 20 25 (SEQ ID NO: 1)

15

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro  
 1 5 10 15

20

Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu Leu Asp Glu Ala  
 20 25 30

25

Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe  
 35 40 45

Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly  
 50 55 60

30

Ser Arg  
 65 (SEQ ID NO: 3)

In accordance with a fifth aspect of the invention, there is provided a composition comprising the C chain of human H3 relaxin, the C chain having the amino acid sequence:

35

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## B Chain

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
1                5                10                15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
20 25

(SEO ID NO: 2)

the A and B chains being linked by disulphide bonds between A11-B10, A24-B22.

10

Human H3 relaxin possesses classical relaxin bioactivity. Human relaxins, H1 and H2 relaxin, bind to cells expressing relaxin receptors, such as THP-1 cells (Parsell et al (1996) *J. Biol. Chem.* 271, 27936-27941). H2 relaxin produces a dose dependent increase in cAMP production from these cells. Synthetic H3 relaxin produced according to this invention stimulated a dose dependent increase in cAMP in keeping with human H2 relaxin. The specificity of response in target cells bearing the human relaxin receptor as exhibited by H3 relaxin is demonstrated by the inability of bovine insulin (bINSL) or human insulin (hINSL3) to stimulate cAMP responses at doses up to 1  $\mu$ M in THP-1 cells.

20 The elicitation of a second messenger response (cAMP) by stimulating human relaxin receptors with human H3 relaxin, provides definitive evidence that human H3 relaxin has classic relaxin biological activity. Such assays in cells containing relaxin receptors, for example THP-1 cells as referred to above provides, a ready way to determine relaxin activity. In addition, the ability of human H3 relaxin to compete with P<sup>32</sup>-labelled H2  
25 relaxin in binding to relaxin binding sites in cells expressing relaxin receptors, again provides definitive confirmation of relaxin activity.

Other biological activities/assays for determining relaxin activity are known in the art. For example, bioassays used for the measurement of active relaxin during pregnancy and non-pregnancy, such as the guinea pig interpubic ligament assay may be used (Steinetz et al 30 (1960) *Endocrinology* 67, 102-115, and Sirosi et al (1983) *American Journal of Obstetrics and Gynaecology* 145: 402-405) may be used. Other bioassays include cAMP production

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in THP-1 cells (Parsell *et al* (1996) J. Biol. Chem 271, 27936-27941).

Applicant has found that H3 relaxin analogues may be prepared where up to 9 amino acids are truncated from the N-terminus of the A chain, and up to 9 amino acids are truncated from the N-terminus of the B chain, and up to 5 amino acids are truncated from the C-terminus of the B chain.

The resulting relaxin analogues comprise a H3 relaxin A and B chain, the A chain having the amno acid sequence

10

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser  
1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys

15

20

(SEQ ID NO: 4)

truncated by up to about 9 amino acids from amino-terminus,

and the B chain having the amino acid sequence:

20

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
1                5                      10                          15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

25

20

25

(SEQ ID NO: 2)

truncated by up to 9 amino acids from the amino-terminus and/or up to about 5 amino acids from the carboxyl-terminus,

the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity. The A chain of human H3 relaxin contains an intrachain disulphide bond between Cys residues 10 and 15.



- 19 -

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
 1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
 5 20 25 (SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

10 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin analogue has relaxin bioactivity.

The isolation, purification and characterisation of nucleic acid sequences encoding human H3 relaxin has allowed the characterisation and production of the signal sequence of  
 15 human H3 relaxin, and the pro-sequence of human H3 relaxin.

The identification, purification and characterisation of the signal sequence and C chain of human H3 relaxin enables the prepro- and pro-human H3 relaxin to be produced.

20 In accordance with another aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

25 the A chain comprising:

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser  
 1 5 10 15

30 Lys Ser Glu Ile Ser Ser Leu Cys  
 20 (SEQ ID NO: 4)

- 20 -

the B chain comprising:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
 1 5 10 15  
 5  
 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
 20 25 (SEQ ID NO: 2)

the signal sequence comprising:

10  
 Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Leu Thr  
 1 5 10 15  
 Gly Glu Leu Trp Pro Gly Ala Glu Ala  
 15 20 25 (SEQ ID NO: 1)

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro  
 20 1 5 10 15  
 Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu Leu Asp Glu Ala  
 20 25 30  
 25 Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe  
 35 40 45  
 Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly  
 51 55 60  
 30  
 Ser Arg  
 65 (SEQ ID NO: 3)

In accordance with a further aspect of the invention there is provided the C chain of human  
 35 H3 relaxin, said C chain having the amino acid sequence:

Fig. 1A

**A: H3 relaxin assembled gene sequence**

**TATAAATGGGGGGCCAAGAGGCAGCAGAGACACTGGCCCACTCTCACGTTCAAAGCGTCT**  
**CCGTCCAGCATGGCCAGGTACATGCTGCTGCTGCTCCTGGCGGTATGGGTGCTGACCGGG**  
**M A R Y M L L L L L A V W V L T G**  
**Signal peptide**  
**GAGCTGTGGCCGGGAGCTGAGGCCCGGGCAGCGCCTTACGGGGTCAGGCTTTGCGGCCGA**  
**E L W P G A E A R A A P Y G V R L C G R**  
**GAATTCATCCGAGCAGTCATCTTCACCTGCGGGGGCTCCCGGTGGAGACGATCAGACATC**  
**E F I R A V I F T C G G S R W R R S D I**  
**B Chain**  
**CTGGCCACGAGGCTATGG>gtgaggctggggagagagtggatgtagaaggggaacag-**  
**L A H E A M**  
  
**-----intron 2318bp-----**  
**-cactaactctgttcacatcttttgag<GAGATACCTTCCCGGATGCAGATGCTGATGAA**  
**G D T F P D A D A D E**  
  
**GACAGTCTGGCAGGCGAGCTGGATGAGGCCATGGGGTCCAGCGAGTGGCTGGCCCTGACC**  
**D S L A G E L D E A M G S S E W L A L T**  
**C Chain**  
**AAGTACCCCAAGGCCTTTTACAGGGGGCGACCCAGCTGGCAAGGAACCCCTGGGGTTCTT**  
**K S P Q A F Y R G R P S W Q G T P G V L**  
  
**CGGGGCAGCCGAGATGTCTGGCTGGCCTTTCCAGCAGCTGCTGCAAGTGGGGGTGTAGC**  
**R G S R D V L A G L S S S C C K W G C S**  
**A Chain**  
**AAAAGTGAAATCAGTAGCCTTTGCTAGTTTGAGGGCTGGGCAGCCGTGGGCACCAGGACC**  
**K S E I S S L C \***  
  
**AATGCCCCAGTCCTGCCATCCACTCAACTAGTGTCTGGCTGGGCACCTGTCTTTTCGAGCC**  
**TCACACATTCAATTCATTCATCTACAAGTCACAGAGGCACTGTGGGCTCAGGCACAGTCTC**  
**CCGACACCACCTATCCAACCCTGCCCTTTGACCAGCCTATCATGACCCTGGCCCCCTAAGG**  
**AAGCTGTGCCCCCTGCCTGGTCAAGTGGGGACCCCCCATCCTGACCCCTGACCTCTCCCC**  
**AGCCCTAACCATGCGTTTGCCTGGCCTACACACTCCACTGCCACAACCTGGGTCCCTACTC**  
**TACCTAGGCTGGCCACACAGAGACCCCTGCCCCCTTCCAGTCCAAACTGTGGCCATTGT**  
**CCCCTGACCAGCTAAAATCAAGCCTCTGTCTCAGTCCAGCCTTTGCACGCACGCTTCCTT**  
**TGCCCTGCTTTCCATCCCCCTCTCCCTCCAACCTCCCCTGCCAGAGTTCCAAGGCTGTGGAC**  
**CCCAGAGAAGGTGGCAGGTGGCCCCCCTAGGAGAGCTCTGGGCACATTGCAATCTTCCCA**  
**AACTCCAATAATAAAATTGCAAGACTTTGGCAGAGAGTGTGTGTGTGTGTATGGTTG**

Fig. 2A

A.

## B Chain Aligns

	1	5	10	15	20	25
Human 1	KWKDDVIKLCGRELVRAQIAICGMSTWS					
Human 2	DSWMEEVIKLCGRELVRAQIAICGMSTWS					
Cons 1,2,3	.....++LCGRE.+RA.I..CG.S.W.					
Human 3	RAAPYGVRLCGREFIRAVIFTCGGSRW					
Cons 3	R.APYGV+LCGREFIRAVIFTCGGSRW					
Mouse 3	RPAPYGVKLCGREFIRAVIFTCGGSRW					
Cons Mouse	.....+++CGRE+.R.+I..CG.S..					
Mouse 1	RVSEEWMDGFIRMCGREYARELIKICGASVGRAL					

## A Chain Aligns

	1	5	10	15	20
Human 1	RPYVALFEKCCLIGCTKRSLAKYC				
Human 2	QLYSALANKCCHVGCTKRSLARFC				
Cons 1,2,3	...+.L...CC..GC+K...+...C				
Human 3	DVLAGLSSSCCKWGCSKSEISSL				
Cons 3	DVLAGLSSSCC+WGCSKS+ISSLC				
Rat 3	DVLAGLSSSCCEWGCSKSQISSL				
Mouse 3	DVLAGLSSSCCEWGCSKSQISSL				
Cons Mouse	+.....S...CC..GCS+...I..L-C				
Mouse 1	ESGGLMSQQCCHVGCSRRSIKLYC				

## SEQUENCE LISTING

<110> Howard Florey Institute of Experimental Physiology  
and Medicine  
5 University of Melbourne

<120> H3 Relaxin

<130> 7640120/PAS  
10

<160> 10

<170> PatentIn version 3.0

15 <210> 1  
<211> 25  
<212> PRT  
<213> H3-signal

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1 5 10 15  
Gly Glu Leu Trp Pro Gly Ala Glu Ala  
20 25

25 <210> 2  
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<212> PRT  
<213> H3-B chain

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Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg  
1 5 10 15  
Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp  
35 20 25

<210> 3



PubMed

Nucleotide

Protein

Genome

Structure

PMC

Taxonomy

OMIM

Books

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History

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Details

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Range: from begin

to end

Features: ☒ CDD

+

Refresh

☐ 1: Q8WXF3. Reports Relaxin-3 precurs...[gi:37999891]BLink, Conserved  
Domains, Links

Comment Features Sequence

LOCUS Q8WXF3 142 aa linear PRI 20-FEB-2007

DEFINITION Relaxin-3 precursor (Prorelaxin H3) (Insulin-like peptide INSL7) (Insulin-like peptide 7) [Contains: Relaxin-3 B chain; Relaxin-3 A chain].

ACCESSION Q8WXF3

VERSION Q8WXF3 GI:37999891

DBSOURCE swissprot: locus REL3\_HUMAN, accession [Q8WXF3](#); class: standard.  
extra accessions: Q6UXW5  
created: Oct 10, 2003.  
sequence updated: Mar 1, 2002.  
annotation updated: Feb 20, 2007.  
xrefs: [AF447451.1](#), [AAL40345.1](#), [AB076563.1](#), [BAC53758.1](#), [AY358181.1](#), [AAQ88548.1](#), [2FHWA](#), [2FHWA](#)  
xrefs (non-sequence databases): UniGene:Hs.352155, Ensembl:ENSG00000171136, KEGG:hsa:117579, HGNC:17135, MIM: [606855](#), ArrayExpress:Q8WXF3, GermOnline:ENSG00000171136, RZPD-ProtExp:T3225, InterPro:IPR004825, SMART:SM00078, PROSITE:PS00262

KEYWORDS 3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal.

SOURCE Homo sapiens (human)

ORGANISM [Homo sapiens](#)  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo.

REFERENCE 1 (residues 1 to 142)

AUTHORS Holloway, J.L., Lok, S. and Jaspers, S.R.

TITLE Direct Submission

JOURNAL Submitted (??-NOV-2001)

REMARK NUCLEOTIDE SEQUENCE [MRNA].

REFERENCE 2 (residues 1 to 142)

AUTHORS Kizawa, H., Nishi, K., Ishibashi, Y., Harada, M., Asano, T., Ito, Y., Suzuki, N., Hinuma, S., Fujisawa, Y., Onda, H., Nishimura, O. and Fujino, M.

TITLE Production of recombinant human relaxin 3 in AtT20 cells

JOURNAL Regul. Pept. 113 (1-3), 79-84 (2003)

PUBMED [12686464](#)

REMARK NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-127.

REFERENCE 3 (residues 1 to 142)

AUTHORS Clark, H.F., Gurney, A.L., Abaya, E., Baker, K., Baldwin, D., Brush, J.,

Chen,J., Chow,B., Chui,C., Crowley,C., Currell,B., Deuel,B., Dowd,P., Eaton,D., Foster,J., Grimaldi,C., Gu,Q., Hass,P.E., Heldens,S., Huang,A., Kim,H.S., Klimowski,L., Jin,Y., Johnson,S., Lee,J., Lewis,L., Liao,D., Mark,M., Robbie,E., Sanchez,C., Schoenfeld,J., Seshagiri,S., Simmons,L., Singh,J., Smith,V., Stinson,J., Vagts,A., Vandlen,R., Watanabe,C., Wieand,D., Woods,K., Xie,M.H., Yansura,D., Yi,S., Yu,G., Yuan,J., Zhang,M., Zhang,Z., Goddard,A., Wood,W.I., Godowski,P. and Gray,A.

TITLE The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment

JOURNAL Genome Res. 13 (10), 2265-2270 (2003)

PUBMED [12975309](#)

REMARK NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].  
Erratum:[Genome Res. 2003 Dec;13(12):2759]

REFERENCE 4 (residues 1 to 142)

AUTHORS Sudo,S., Kumagai,J., Nishi,S., Layfield,S., Ferraro,T., Bathgate,R.A. and Hsueh,A.J.

TITLE H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both the ectodomain and the exoloop 2

JOURNAL J. Biol. Chem. 278 (10), 7855-7862 (2003)

PUBMED [12506116](#)

REMARK INTERACTION WITH LGR7.

REFERENCE 5 (residues 1 to 142)

AUTHORS Liu,C., Eriste,E., Sutton,S., Chen,J., Roland,B., Kuei,C., Farmer,N., Jornvall,H., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein-coupled receptor GPCR135

JOURNAL J. Biol. Chem. 278 (50), 50754-50764 (2003)

PUBMED [14522968](#)

REMARK INTERACTION WITH GPCR135.

REFERENCE 6 (residues 1 to 142)

AUTHORS Liu,C., Chen,J., Sutton,S., Roland,B., Kuei,C., Farmer,N., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as a ligand for GPCR142

JOURNAL J. Biol. Chem. 278 (50), 50765-50770 (2003)

PUBMED [14522967](#)

REMARK INTERACTION WITH GPCR142.

COMMENT [FUNCTION] May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin-3 receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).  
[SUBUNIT] Heterodimer of a B chain and an A chain linked by two disulfide bonds.  
[SUBCELLULAR LOCATION] Secreted protein.  
[SIMILARITY] Belongs to the insulin family.

FEATURES

source	Location/Qualifiers
	1..142
	/organism="Homo sapiens"
	/db_xref="taxon:9606"
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	/note="synonyms: INSL7, RXN3, ZINS4"
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	/product="Relaxin-3 precursor"
Region	1..25
	/gene="RLN3"
	/locus_tag="UNQ6188/PRO20213"

Region /region\_name="Signal"  
/experiment="experimental evidence, no additional details recorded"  
26..52  
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/locus\_tag="UNQ6188/PRO20213"  
/region\_name="IIGF"  
/note="Insulin / insulin-like growth factor / relaxin family; insulin family of proteins; groups a number of active peptides which are evolutionary related including insulin, relaxin, insulin-like growth factors I and II, mammalian Leydig cell-specific insulin-like peptide (gene INSL3), and early placenta insulin-like peptide (ELIP) (gene INSL4), insect prothoracicotropic hormone (bombyxin), locust insulin-related peptide (LIRP), molluscan insulin-related peptides 1 to 5 (MIP), and C; cd00101"  
/db\_xref="CDD:58309"

Bond bond(35,129)  
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/note="Interchain (between B and A chains) (By similarity)."

Region 36  
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/experiment="experimental evidence, no additional details recorded"

Region 37..47  
/gene="RLN3"  
/locus\_tag="UNQ6188/PRO20213"  
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Bond bond(47,142)  
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/inference="non-experimental evidence, no additional details recorded"  
/note="Interchain (between B and A chains) (By similarity)."



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 /FTId=PRO\_0000016083."

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 /note="Relaxin-3 A chain (By similarity)."  
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 /experiment="experimental evidence, no additional details recorded"

Bond bond(128,133)  
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 /locus\_tag="UNQ6188/PRO20213"  
 /bond\_type="disulfide"  
 /inference="non-experimental evidence, no additional details recorded"  
 /note="By similarity."

Region 131  
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 /locus\_tag="UNQ6188/PRO20213"  
 /region\_name="Hydrogen bonded turn"  
 /experiment="experimental evidence, no additional details recorded"

Region 135..139  
 /gene="RLN3"  
 /locus\_tag="UNQ6188/PRO20213"  
 /region\_name="Helical region"  
 /experiment="experimental evidence, no additional details recorded"

Region 140..141  
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## ORIGIN

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121 laglssscck wgcskseiis lc

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//

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Feb 20 2007 16:53:14

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UniProtKB Entry

PIR View

UniProtKB Entry: **Q8WXF3**

ENTRY INFORMATION	
ENTRY NAME	REL3_HUMAN
ACCESSION NUMBERS	Q8WXF3; Q6UXW5
Integrated into Swiss-Prot on	2003-10-10
Sequence was last modified on	2002-03-01 (Sequence version 1)
Annotations were last modified on	2007-02-20 (Entry version 47)
NAME AND ORIGIN OF THE PROTEIN	
PROTEIN NAME	Relaxin-3 precursor
Synonyms	Prorelaxin H3 Insulin-like peptide INSL7 Insulin-like peptide 7
Contains	Relaxin-3 B chain Relaxin-3 A chain
GENE NAME	Name: RLN3 Synonym: INSL7; RXN3; ZINS4 ORF name: UNQ6188/PRO20213
SOURCE ORGANISM	Homo sapiens
TAXONOMY ID	9606 [NCBI, NEWT]
LINEAGE	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
REFERENCES	
[1]	Holloway JL; Lok S; Jaspers SR. <b>Homo sapiens insulin homolog polypeptide.</b> Submitted (NOV-2001) to EMBL/GenBank/DDBJ databases. <i>Position:</i> NUCLEOTIDE SEQUENCE [MRNA].
[2]	Kizawa H; Nishi K; Ishibashi Y; Harada M; Asano T; Ito Y et al. View <b>Production of recombinant human relaxin 3 in AtT20 cells.</b> 2003, <i>Regul. Pept.</i> , 113, 79-84.

	<i>Position:</i> NUCLEOTIDE SEQUENCE [MRNA]; PROTEIN SEQUENCE [MRNA] <i>PubMed:</i> 12686464; <i>Medline:</i> 22573778.
[3]	Clark HF; Gurney AL; Abaya E; Baker K; Baldwin DT; Brush J et al. <b>The secreted protein discovery initiative (SPDI), a large-scale effort to identify human transmembrane proteins: a bioinformatics assessment.</b> 2003, <i>Genome Res.</i> , 13, 2265-2270. <i>Position:</i> NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA]. <i>PubMed:</i> 12975309; <i>Medline:</i> 22887296.
[4]	Sudo S; Kumagai J; Nishi S; Layfield S; Ferraro T; Bathgate RAD et al. <b>H3 relaxin is a specific ligand for LGR7 and activates the receptor and the exoloop 2.</b> 2003, <i>J. Biol. Chem.</i> , 278, 7855-7862. <i>Position:</i> INTERACTION WITH LGR7. <i>PubMed:</i> 12506116; <i>Medline:</i> 22499664.
[5]	Liu C; Eriste E; Sutton S; Chen J; Roland B; Kuei C et al. <a href="#">View all</a> . <b>Identification of relaxin-3/INSL7 as an endogenous ligand for the GPCR135.</b> 2003, <i>J. Biol. Chem.</i> , 278, 50754-50764. <i>Position:</i> INTERACTION WITH GPCR135. <i>PubMed:</i> 14522968;
[6]	Liu C; Chen J; Sutton S; Roland B; Kuei C; Farmer N et al. <a href="#">View all</a> . <b>Identification of relaxin-3/INSL7 as a ligand for GPCR142.</b> 2003, <i>J. Biol. Chem.</i> , 278, 50765-50770. <i>Position:</i> INTERACTION WITH GPCR142. <i>PubMed:</i> 14522967;

**COMMENTS**

<b>FUNCTION</b>	May play a role in neuropeptide signaling processes. Ligand for LGR7 relaxin-3 receptor-2 (GPCR142).
<b>SUBUNIT</b>	Heterodimer of a B chain and an A chain linked by two disulfide bonds.
<b>SUBCELLULAR LOCATION</b>	Secreted protein.
<b>SIMILARITY</b>	Belongs to the insulin family.

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**DATABASE CROSS-REFERENCES**

<b>ARRAYEXPRESS</b>	Q8WXF3.
<b>EMBL</b>	AF447451,AAL40345.1,mRNA. [GenBank, DDBJ] AB076563,BAC53758.1,mRNA. [GenBank, DDBJ] AY358181,AAQ88548.1,ALT_INIT,mRNA. [GenBank, DDBJ]
<b>ENSEMBL</b>	ENSG00000171136,Homo sapiens.
<b>GERMOnline</b>	ENSG00000171136,Homo sapiens
<b>HGNC</b>	HGNC:17135,RLN3.
<b>INTERPRO</b>	IPR004825,Ins/IGF/relax.

<b>KEGG</b>	hsa:117579.
<b>MIM</b>	606855, gene.
<b>PDB</b>	2FHW, NMR, A=119-142, B=26-52.
<b>PROSITE</b>	PS00262, INSULIN, 1.
<b>RZPD_PROTEXP</b>	T3225
<b>SMART</b>	SM00078, IIGF, 1.
<b>UNIGENE</b>	Hs.352155
<b>UniRef</b>	View cluster of proteins with at least 50% / 90% / 100% identity.

**KEYWORDS**

3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal

**FEATURES**

Feature	Description
SIGNAL PEPTIDE	
PEPTIDE	Relaxin-3 B chain (By similarity). /FTId=PRO_00000
PROPEPTIDE	Connecting peptide (BY SIMILARITY) /FTId=PRO_00000
PEPTIDE	Relaxin-3 A chain (By similarity). /FTId=PRO_00000
DISULFIDE BOND	Interchain (between B and A chains) (BY SIMILARITY
DISULFIDE BOND	Interchain (between B and A chains) (BY SIMILARITY
DISULFIDE BOND	BY SIMILARITY
STRAND	
TURN	
HELIX	
TURN	
HELIX	
TURN	
HELIX	
TURN	

Feature sequence (Put the mouse on the feature above to see the sequence below):

RAAPYGVRLCGREFIRAVIFTCGGSRW

**SEQUENCE**

<b>LENGTH</b>	142 aa
<b>MOLECULAR WEIGHT</b>	15451 Da
<b>CRC64 CHECKSUM</b>	23A3E095034B31E4



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# UniProtKB/Swiss-Prot entry Q8WXF3

[\[Entry info\]](#) [\[Name and origin\]](#) [\[References\]](#) [\[Comments\]](#) [\[Cross-references\]](#)  
[\[Keywords\]](#) [\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

*Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.*

## Entry information

Entry name	<b>REL3_HUMAN</b>
Primary accession number	<b>Q8WXF3</b>
Secondary accession number	Q6UXW5
Integrated into Swiss-Prot on	October 10, 2003
Sequence was last modified on	March 1, 2002 (Sequence version 1)
Annotations were last modified on	February 20, 2007 (Entry version 47)

## Name and origin of the protein

Protein name	<b>Relaxin-3 [Precursor]</b>
Synonyms	<b>Prorelaxin H3</b> <b>Insulin-like peptide INSL7</b> <b>Insulin-like peptide 7</b>

## Contains

**Relaxin-3 B chain**  
**Relaxin-3 A chain**

## Gene name

**Name: RLN3**  
Synonyms: INSL7, RXN3, ZINS4  
ORFNames: UNQ6188/PRO20213

## From

## Taxonomy

Homo sapiens (Human) [TaxID: 9606]  
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata;  
Euteleostomi; Mammalia; Eutheria; Euarchontoglires;  
Primates; Haplorrhini; Catarrhini; Hominidae; Homo.

## References

### [1] NUCLEOTIDE SEQUENCE [MRNA].

Holloway J.L., Lok S., Jaspers S.R.;  
"Homo sapiens insulin homolog polypeptide."  
Submitted (NOV-2001) to the EMBL/GenBank/DDBJ databases.

### [2] NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-12 DOI=10.1016/S0167-0115(02)00304-X; PubMed=12686464 [NCBI, ExPASy, EBI, Israel, .


Kizawa H., Nishi K., Ishibashi Y., Harada M., Asano T., Ito Y., Suzuki N., Hinuma S., Fujis Y., Onda H., Nishimura O., Fujino M.;

"Production of recombinant human relaxin 3 in AtT20 cells.";

Regul. Pept. 113:79-84(2003).

[3] NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA].

DOI=10.1101/gr.1293003; PubMed=12975309 [NCBI, ExPASy, EBI, Israel, Japan]

Clark H.F., Gurney A.L., Abaya E., Baker K., Baldwin D.T., Brush J., Chen J., Chow B., Cl Crowley C., Currell B., Deuel B., Dowd P., Eaton D., Foster J.S., Grimaldi C., Gu Q., Hass Heldens S., , Gray A.M.;

"The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel hum secreted and transmembrane proteins: a bioinformatics assessment.";

Genome Res. 13:2265-2270(2003).

[4] INTERACTION WITH LGR7.

DOI=10.1074/jbc.M212457200; PubMed=12506116 [NCBI, ExPASy, EBI, Israel, Japan]

Sudo S., Kumagai J., Nishi S., Layfield S., Ferraro T., Bathgate R.A.D., Hsueh A.J.W.;

"H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both ectodomain and the exoloop 2.";

J. Biol. Chem. 278:7855-7862(2003).

[5] INTERACTION WITH GPCR135.

DOI=10.1074/jbc.M308995200; PubMed=14522968 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Eriste E., Sutton S., Chen J., Roland B., Kuei C., Farmer N., Joernvall H., Sillard R Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein couple receptor GPCR135.";

J. Biol. Chem. 278:50754-50764(2003).

[6] INTERACTION WITH GPCR142.

DOI=10.1074/jbc.M308996200; PubMed=14522967 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Chen J., Sutton S., Roland B., Kuei C., Farmer N., Sillard R., Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as a ligand for GPCR142.";

J. Biol. Chem. 278:50765-50770(2003).

Comments

- **FUNCTION:** May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin-3 receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).
- **SUBUNIT:** Heterodimer of a B chain and an A chain linked by two disulfide bonds.
- **SUBCELLULAR LOCATION:** Secreted protein.
- **SIMILARITY:** Belongs to the insulin family.

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Cross-references

Sequence databases

EMBL	AF447451; AAL40345.1; -; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AB076563; BAC53758.1; -; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AY358181; AAQ88548.1; ALT_INIT; mRNA.	[EMBL / GenBank / DDBJ] [CoDingSequence]



UniGene Hs.352155

### 3D structure databases

PDB 2FWH; NMR; A=119-142, B=26-52.[ExPASy / RCSB / EBI]

ModBase Q8WXF3.

### Organism-specific gene databases

HGNC HGNC:17135; RLN3.

GeneCards RLN3.

GeneLynx RLN3; Homo sapiens.

GenAtlas RLN3.

MIM 606855; gene. [NCBI / EBI]

HOVERGEN [Family / Alignment / Tree]

### Gene expression databases

CleanEx HGNC:17135; RLN3.

ArrayExpress Q8WXF3; -.

GermOnline ENSG00000171136; Homo sapiens.

### Family and domain databases

InterPro IPR004825; Ins/IGF/relax.  
Graphical view of domain structure.

SMART SM00078; IIGF; 1.  
SMART graphical view of domain structure.

PROSITE PS00262; INSULIN; 1.

ProDom [Domain structure / List of seq. sharing at least 1 domain]

BLOCKS Q8WXF3.

### Genome annotation databases

Ensembl ENSG00000171136; Homo sapiens. [Contig view]

KEGG hsa:117579; -.

### Other

RZPD-  
ProtExp Clones: T3225

SOURCE RLN3; Homo sapiens.

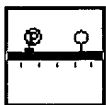
ProtoNet Q8WXF3.

UniRef View cluster of proteins with at least 50% / 90% / 100% identity.

### Keywords

**3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone Signal.**

### Features



Feature table viewer



Feature aligner

Key	From	To	Length	Description	FTId
SIGNAL	1	25	25		
PEPTIDE	26	52	27	Relaxin-3 B chain ( <i>By similarity</i> ).	PRO_000C
PROPEP	55	118	64	Connecting peptide ( <i>By similarity</i> ).	PRO_000C

PEPTIDE	119	142	24	Relaxin-3 A chain ( <i>By similarity</i> ).	PRO_0000
DISULFID	35	129		Interchain (between B and A chains) ( <i>By similarity</i> ).	
DISULFID	47	142		Interchain (between B and A chains) ( <i>By similarity</i> ).	
DISULFID	128	133		By similarity.	
STRAND	29	32	4		
TURN	36	36	1		
HELIX	37	47	11		
TURN	48	48	1		
HELIX	120	130	11		
TURN	131	131	1		
HELIX	135	139	5		
TURN	140	141	2		

**Sequence information**

Length: **142 AA** [This is the length of the unprocessed precursor]

Molecular weight: **15451 Da** [This is the MW of the unprocessed precursor]

CRC64: **23A3E095034B31E**  
is a checksum on the sequence

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<u>70</u>	<u>80</u>	<u>90</u>	<u>100</u>	<u>110</u>	<u>120</u>
EAMGDTFPDA	DADEDSLAGE	LDEAMGSSEW	LALTKSPQAF	YRGRPSWQGT	PGVLRGSRDV
<u>130</u>	<u>140</u>				
LAGLSSSCCK	WGCSKSEISS	LC			

Q8WXF3  
in  
F00000  
for

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ExPASy/SIB  
or at NCBI (USA)



Sequence analysis tools: ProtParam,  
ProtScale, Compute pI/Mw, PeptideMass,  
PeptideCutter, Dotlet (Java)



ScanProsite, MotifScan



Submit a homology modeling request to  
SWISS-MODEL



NPSA Sequence  
analysis tools



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for Q8WXF3

# UniProtKB/Swiss-Prot: Q8WXF3 (REL3\_HUMAN)

The section of the sequence Q8WXF3 (REL3\_HUMAN) you have selected corresponds to:

PEPTIDE      26      52      Relaxin-3 B chain (By similarity).  
/FTid=PRO\_0000016082.

In one-letter code:

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1  MARYMLLLLL AVWVLTGELW PGAEARAAPY GVRLCGREFI RAVIFTCGGS RWRRSDI
61 EAMGDTFPDA DADEDSLAGE LDEAMGSSEW LALTKSPQAF YRGRPSWQGT PGVLRGSI
121 LAGLSSSCCK WGCSKSEISS LC

```

In three-letter code:

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      1   2   3   4   5   6   7   8   9  10  11  12  13  14  15
1  Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Leu
16 Thr Gly Glu Leu Trp Pro Gly Ala Glu Ala Arg Ala Ala Pro Tyr
31 Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg Ala Val Ile Phe
46 Thr Cys Gly Gly Ser Arg Trp Arg Arg Ser Asp Ile Leu Ala His
61 Glu Ala Met Gly Asp Thr Phe Pro Asp Ala Asp Ala Asp Glu Asp
76 Ser Leu Ala Gly Glu Leu Asp Glu Ala Met Gly Ser Ser Glu Trp
91 Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe Tyr Arg Gly Arg Pro
106 Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly Ser Arg Asp Val
121 Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser Lys
136 Ser Glu Ile Ser Ser Leu Cys

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Direct similarity search submission of this **subsequence** to

**BLAST**

BLAST submission on  
ExPASy/SIB  
or at NCBI (USA)



Sequence analysis tools: ProtParam,  
ProtScale, Compute pI/Mw, PeptideMass,  
PeptideCutter, Dotlet (Java)



ScanProsite



Direct Submission to SWISS-MODEL

**NPS@** NPSA Sequence  
analysis tools



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**Swiss-Prot**

## SEQUENCE LISTING

<110> Del Borgo, Mark  
 Wade, John D.  
 Bathgate, Ross D.  
 Hughes, Richard A.  
 Howard Florey Institute of Physiology and Medicine  
 The University of Melbourne

<120> Relaxin Superfamily Peptide Analogues

<130> 087521-000000US

<140> US 10/561,304  
 <141> 2005-12-19

<150> AU 2003903124  
 <151> 2003-06-20

<150> WO PCT/AU04/00798  
 <151> 2004-06-18

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&lt;220&gt;

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&lt;400&gt; 7

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&lt;210&gt; 8

&lt;211&gt; 33

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&lt;220&gt;

&lt;223&gt; insulin-like 4 (INSL4) b-chain

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 20 25 30

Pro

&lt;210&gt; 9

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; insulin-like 5 (INSL5) b-chain

&lt;400&gt; 9

Val Arg Ser Lys Glu Ser Val Arg Leu Cys Gly Leu Glu Tyr Ile Arg  
 1 5 10 15

Thr Val Ile Tyr Ile Cys Ala Ser Ser Arg Trp Arg Arg His Leu Glu  
 20 25 30

Gly

<210> 10  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> insulin-like 6 (INSL6) b-chain

<400> 10  
 Ser Asp Ile Ser Ser Ala Arg Lys Leu Cys Gly Arg Tyr Leu Val Lys  
           1                  5                  10                  15

Glu Ile Glu Lys Leu Cys Gly His Ala Asn Trp Ser Gln Phe Arg Phe  
                   20                  25                  30

Glu

<210> 11  
 <211> 25  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:cyclic relaxin  
           b-chain mimetic (cRLx)

<220>  
 <221> DISULFID  
 <222> (2)..(24)

<400> 11  
 Ser Cys Met Glu Glu Val Ile Lys Leu Ser Gly Arg Glu Leu Val Arg  
           1                  5                  10                  15

Ala Gln Ile Ala Ile Ser Gly Cys Ser  
                   20                  25

<210> 12  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:insulin-like 3  
           (INSL3) b-chain peptide analogue 4, cyclic peptide  
           cINSL3a

<220>  
 <221> DISULFID  
 <222> (3)..(25)

<400> 12  
 Thr Pro Cys Met Arg Glu Lys Leu Ser Gly His His Phe Val Arg Ala  
           1                  5                  10                  15

Leu Val Arg Val Ser Gly Gly Pro Cys Trp Ser  
                   20                  25



<210> 13  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:insulin-like 3  
 (INSL3) b-chain peptide analogue 5, cyclic peptide  
 cINSL3b

<220>  
 <221> DISULFID  
 <222> (3)..(25)

<400> 13  
 Thr Pro Cys Met Arg Glu Lys Leu Ser Gly Arg His Phe Val Arg Ala  
           1                          5                          10                          15  
 Leu Val Arg Val Ser Gly Gly Pro Cys Trp Ser  
                           20                          25

<210> 14  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:insulin-like 3  
 (INSL3) b-chain peptide analogue 6

<400> 14  
 Thr Pro Cys Met Arg Glu Lys Leu Ser Gly Arg Glu Leu Val Arg Ala  
           1                          5                          10                          15  
 Gln Val Ile Ala Ile Gly Gly Pro Cys Trp Ser  
                           20                          25

<210> 15  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:insulin-like 3  
 (INSL3) b-chain peptide analogue 7

<400> 15  
 Thr Cys Glu Met Arg Glu Lys Leu Ser Gly His His Phe Val Arg Ala  
           1                          5                          10                          15  
 Leu Val Arg Val Ser Gly Gly Cys Arg Trp Ser  
                           20                          25

<210> 16  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<220>

<223> relaxin-1 a-chain

<400> 16

Arg	Pro	Tyr	Val	Ala	Leu	Phe	Glu	Lys	Cys	Cys	Leu	Ile	Gly	Cys	Thr
1				5				10						15	

Lys	Arg	Ser	Leu	Ala	Lys	Tyr	Cys
			20				

<210> 17

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-2 a-chain

<400> 17

Gln	Leu	Tyr	Ser	Ala	Leu	Ala	Asn	Lys	Cys	Cys	His	Val	Gly	Cys	Thr
1				5				10						15	

Lys	Arg	Ser	Leu	Ala	Arg	Phe	Cys
			20				

<210> 18

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-3 a-chain

<400> 18

Asp	Val	Leu	Ala	Gly	Leu	Ser	Ser	Ser	Cys	Cys	Lys	Trp	Gly	Cys	Ser
1				5					10					15	

Lys	Ser	Glu	Ile	Ser	Ser	Leu	Cys
			20				

<210> 19

<211> 26

<212> PRT

<213> Homo sapiens

<220>

<223> insulin a-chain

<400> 19

Ser	Leu	Gln	Lys	Arg	Gly	Ile	Val	Glu	Gln	Cys	Cys	Thr	Ser	Ile	Cys
1				5				10						15	

Ser	Leu	Tyr	Gln	Leu	Glu	Asn	Tyr	Cys	Asn
			20					25	

<210> 20  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> insulin-like growth factor 1 (IGF-1) a-chain

<400> 20  
 Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp  
           1                  5                  10                  15  
 Leu Arg Arg Leu Glu Met Tyr Cys Ala  
                   20                  25

<210> 21  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> insulin-like growth factor 2 (IGF-2) a-chain

<400> 21  
 Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys Asp  
           1                  5                  10                  15  
 Leu Ala Leu Leu Glu Thr Leu Cys Ala  
                   20                  25

<210> 22  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> insulin-like 3 (INSL3) a-chain (Leydig  
           insulin-like (Ley I-L)/relaxin like factor (RLF))

<400> 22  
 Ala Ala Ala Thr Asn Pro Ala Arg Tyr Cys Cys Leu Ser Gly Cys Thr  
           1                  5                  10                  15  
 Gln Gln Asp Leu Leu Thr Leu Cys Pro Tyr  
                   20                  25

<210> 23  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> insulin-like 4 (INSL4) a-chain (placentin/early  
           placenta insulin-like (EPIL))

<400> 23

Arg Ser Gly Arg His Arg Phe Asp Pro Phe Cys Cys Glu Val Ile Cys  
 1 5 10 15

Asp Asp Gly Thr Ser Val Lys Leu Cys  
 20 25

<210> 24

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> insulin-like 5 (INSL5) a-chain

<400> 24

Met Ser Arg Gln Asp Leu Gln Thr Leu Cys Cys Thr Asp Gly Cys Ser  
 1 5 10 15

Met Thr Asp Leu Ser Ala Leu Cys  
 20

<210> 25

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> insulin-like 6 (INSL6) a-chain

<400> 25

Arg Lys Arg Arg Gly Tyr Ser Glu Lys Cys Cys Leu Thr Gly Cys Thr  
 1 5 10 15

Lys Glu Glu Leu Ser Ile Ala Cys  
 20